

REMARKS

Reconsideration and allowance are respectfully requested.

Remarks Regarding Claim Amendments

Claims 1-7, 11-12, 15 and 17-28 and 30 are pending. Claims 1 and 4 have been amended to remove references to reactions using wildtype acylase. Support for the amendments to claim 19, 24 and 26 may be found on page 8, lines 6-7. Claim 29 is canceled.

No new matter is introduced by these claim amendments and their entry is requested.

Remarks Regarding Section 103

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See *id.* at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396.

Claims 1-7, 11-12, 15, 17, 19-21 and 29 stand rejected under 35 U.S.C. 103 as allegedly unpatentable over WO99/31109. Applicants traverse.

The claimed invention and WO99/31109 represents two patentably distinct methods of solving a technical problem. The technical problem is how to obtain an enzymatic acylation reaction with a higher synthesis/hydrolysis ration (S/H ratio). WO99/31109 provides an enzymatic process in the presence of the complexing agents 1-naphtol and 2-naphtol using wild type E. coli acylase. In WO99/31109, the reaction was carried out at 10°C to solve the problem.

A number of significant differences exist between the claimed invention and WO99/31109. These differences are enumerated in the chart below:

Chart 1

Difference Between the Claimed Invention and WO99/31109

	Claim 1	Example IV of WO99/31109
Cephalosporin	Cephadrine	Cefaclor
Final Product	Cephadrine	Cefaclor complexed with 1-naphtol or 2-naphtol
Recovery step from the complex necessary to obtain "free" cephalosporin	Not necessary	Yes - known in the art. See paragraph spanning pages 2 and 3.
Reactant 1 - nucleus	7-ADCA	7-ACCA
Reactant 2 - acylating agent	DH-PGa	PGA
Temperature	At least 15°C	10°C
Hydrolysis product	DH<2 wt%	Not specified
Enzyme used	Acylase with higher S/H ratio than wild type acylase of E. coli	wild type acylase of E. coli

In contrast to the method disclosed in WO99/31109, the claimed invention provides a process performed at a temperature of at least 15°C. Significantly, the claimed invention, in contrast to WO99/31109, does not use wild type E. coli acylase. In

addition, the claimed invention uses an acylase which has a higher synthesis/hydrolysis ratio (S/H ratio) compared to the wild type acylase of *E. coli*.

Since the solution provided by the claimed invention (including, at least, not using wildtype *E. coli* acylase and performing the reaction in at least 15°C) is not disclosed or rendered obvious by WO99/31109, the claimed invention is not obvious in view of WO99/31109.

The withdrawal of this rejection is requested for the above stated reasons.

Remarks Regarding Section 112 Second Paragraph

Claims 1-7, 11-12, 15, 17-30 stand rejected under 35 U.S.C. 112 second paragraph as allegedly indefinite. Applicants traverse each of the rejections made under this section. Each basis for rejection is addressed below in the order presented in the Office Action.

1. The Office Action asserts that “15°” inserted into claim 4 is in error since claim 1 recites below 15°. Solely to expedite prosecution, and without addressing the merits of the Office Action’s position, Applicants have amended claims 1 and 4 so they no longer refer to temperatures below 15° C. Thus, this rejection is moot and its withdrawal is requested.

2. The Office Action asserts that claim 29 is indefinite. Solely to expedite prosecution, and without addressing the merits of the Office Action’s position, Applicants have canceled claim 29. Thus, this rejection is moot and its withdrawal is requested.

3. Claim 1 is allegedly indefinite because it is unclear whether D-dihydrophenylglycine (DH) in the reaction mixture is below 2wt. % throughout the reaction. Solely to expedite prosecution, and without addressing the merits of the Office Action’s position, Applicants have amended claim 1 to clearly state that D-dihydrophenylglycine (DH) in the reaction mixture is below 2wt. % throughout the reaction. Thus, this rejection is moot and its withdrawal is requested.

4. Claim 1 is allegedly indefinite because the “S/H” limitation is indefinite. The Office Action asserts that “S/H” is indefinite because it depends on temperature and

pH. Applicants note that claim 1 recites “an acylase having a higher S/H ratio than the wild type acylase of *E. coli* throughout the reacting step.” Therefore, the temperature and pH necessarily would be the temperature and pH of the reaction and this phrase refers only to an acylase having a higher S/H ratio throughout the conditions of a reaction. Since the reaction conditions are defined, this phrase is not indefinite. Withdrawal of this rejection is requested.

5. Claim 22 is allegedly indefinite because 0% is indefinite. Applicants note that claim 22 depends of claim 1 and incorporate the recitations of claim 1. Claim 1 recites the presence of 7-ADCA so 7-ADCA cannot be zero percent. One of skill in the art, reading claim 22 in the context of claim 1, would understand that it refers to the presence of some 7-ADCA. For this reason, withdrawal of this rejection is requested.

Remarks Regarding Section 112 First Paragraph

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 19-21, 23 and 29 stand rejected under 35 U.S.C. 112 first paragraph as allegedly failing to comply with the enablement requirement. Also, claims 24-26 stand rejected under 35 U.S.C. 112 first paragraph as allegedly failing to comply with the enablement requirement. Specifically, it is alleged that the Specification enables only crystallizing cephradine monohydrates while the claims are not limited to such. Applicants traverse.

Solely to expedite prosecution, Applicants have amended claim 19 to recite “cephradine hydrate with a water content between 3% and 6% by weight.” It is generally known that cephradine may crystallize with non-stoichiometric amounts of

water. For instance, cephadrine monohydrate has a water content of 4.9% and cephadrine dehydrate has a water content of 9.4%. In other words, cephadrine monohydrate contains a water content that is between 3% and 6% by weight while cephadrine dehydrate contains a water content that is not between 3% and 6% by weight.

For the reasons stated above, this rejection is moot in view of Applicants' amendment and its withdrawal is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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